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The U. S. Army Reactive Topical Skin Protectant (rTSP): Challenges and Successes[+♦]

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ABSTRACT

In 1994, the U. S. Army initiated a research effort towards an effective material that acts both as a protective barrier and as an active destructive matrix against chemical warfare agents (CWA). We report results on our preparation and evaluation of Reactive Topical Skin Protectants (rTSP's). These creams are composite materials consisting of a base material (TSP) and a reactive moiety. Using an established base of perfluorinated-polyether and perfluoropolyethylene solids we incorporated over 60 reactive components. Classes tested include organic polymers, organic/inorganic hybrid materials, polyoxometallates (POM's), enzymes, inorganic oxides, metal alloys and small molecules. We characterized these materials by light microscopy and FTIR. We determined the efficacy of these materials against both sulfur mustard (HD) and a representative nerve agent, soman (GD), using a penetration cell model coupled to a continuous air monitor and also by *in vivo* testing. Composite materials with optimum reactive compounds exhibit a 94% reduction of GD vapor break-through after 20 hours (from 9458 ng to 581 ng) and a 3.6 fold increase (from 162 min to 588 min) in the time 1000 ng of GD liquid penetrates through the material. Similar composite materials show a 99% reduction in HD vapor break-through after 20 hours (from 4040 ng to 16 ng), a 2.3 fold increase (from 524 min to >1200 min) in the time 1000 ng of HD vapor penetrates through the material, and an elimination of erythema versus control in an HD vapor challenge. These results indicate that an rTSP that protects against sulfur mustard and nerve agents is within reach.

INTRODUCTION

Chemical warfare agents (CWA's) represent a real and growing threat both to U.S. Armed Forces as well as to civilians. Within the last three decades, chemical weapons have been used by the Soviets in Cambodia (yellow rain, tricothecene mycotoxins) [1], by Iraq against Iran (HD and tabun) [2], and by Iraq against its own dissident Kurdish population at Halabja (HD, $HCN_{(g)}$) [3]. In the United States' experience in World War I, almost one-third of hospitalized casualties were a result of CWA's [4]. Furthermore, the 1995 use of sarin in a terrorist attack in Tokyo, Japan, which resulted in over 1000 casualties and 12 deaths [5], demonstrates that the civilian population has also become a target.

The United States Army classifies CWA's into seven categories [6]. However, in this paper we will focus only on protection against two classes: nerve agents (soman, GD) and blister agents (sulfur mustard, HD). Currently, protection against these agents in the United States Army consists of a chemically resistant outer layer of clothing (BDO) and protective mask (M40) [7]. This scheme of protection does allow continued operation in a chemically contaminated area but results in decreased performance as well as increased heat retention. In a continuing effort to develop a barrier to CWA's that will increase protection without degrading performance, we have investigated a material that serves as a physical barrier to these agents *and* contains an active moiety to neutralize any chemicals that contact this material. This Reactive

Topical Skin Protectant (rTSP) would be used in conjunction with other protective procedures. Herein we report the preparation, characterization, and evaluation of rTSP's.

EXPERIMENTAL DETAILS

Polytetrafluoroethylene (PTFE) resin (Polymist F®) and propene hexafluoro oxidized polymerized oil (Fomblin®) were obtained from Ausimont USA Inc. (Thorofare, NJ). Proprietary reactive moieties were received from extramural contractors through Small Business Innovation Research (SBIR) contracts or direct support of academic investigators. S-330 (1,3,4,6-tetrachloro-7, 8-diimino glycouril) was obtained from Monsanto and used without further purification. Iodobenzene diacetate (IBDA) and diisopropylfluorophosphate (DFP) were purchased from Aldrich Chemical Company. Ambergard® XE-555 resin was obtained from Rohm and Haas Co. (Philadelphia, PA) as part of a M-291 Decontamination Kit. Sulfur Mustard (HD, bis-(2-chlorethyl) sulfide) and soman (GD, pinacolyl methyl phosphonofluoridate) were obtained from Edgewood Research and Development and Engineering Center (ERDEC). NMR spectra were recorded on a Varian Unity INOVA NMR at the appropriate frequency (^{1}H: 600 MHz, ^{13}C: 150 MHz, ^{31}P 242 MHz). FTIR spectra were run on a Nicolet 360 Avatar FTIR system. Experimental details of the *in vitro* and *in vivo* analysis of rTSP's have been reported previously [8].

Formulation of rTSP's followed as closely as possible the technique used for the production of a *non*-reactive topical skin protectant (TSP) base cream [9]. In general, the reactive moiety is suspended in either Fomblin® or Polymist F® by mechanical or manual stirring. The other polymer is added in portions with vigorous mechanical stirring. As a representative example, Polymist F® and S-330 were premixed by hand. Into a white polypropylene container is added Fomblin.® To the clear, colorless liquid the mixture of PTFE and S-330 is added in two portions. After each addition, the opaque tan suspension is agitated by a mechanical stirrer for 5 minutes resulting in a smooth, off-white cream. The container is closed and sealed with parafilm to exclude moisture.

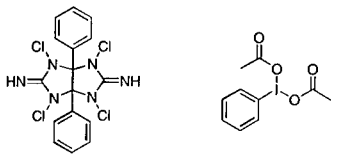
RESULTS

Two criteria constrain our selection of reactive components. First, the barrier properties of the base cream must not be degraded by the incorporation of the compound(s). Second, the reactive moiety must neutralize CWA's in the environment of the base cream (perfluorinated polyether/PTFE). We have investigated over 60 reactive moieties (Table I).

Table I. Classes of Reactive Moieties.

Class of Reactive	Example
Organic Molecule	S-330, Iodobenzenediacetate
Inorganic Compounds	Polymer coated metal alloys (TiFeMn, MgNi, CaNi), Nanoscale metal oxides (MgO, CaO, TiO_2), Polyoxometallates
Organic polymers	Dendrimers, Bridged Polysilsesquioxanes, XE-555 resin
Enzymes	Organophosphorous Acid Anhydride Hydrolase (OPAA) Crosslinked Enzyme Crystals (CLEC's)

These compounds have been formulated into over 200 rTSP's and have been evaluated by both *in vivo* and *in vitro* testing. Among these reactive compounds, two oxidizing organic compounds, S-330 and IBDA, have shown particular efficacy against sulfur mustard (HD) (Figure 1).



S-330 **IBDA**

Figure 1. Organic Reactive Moieties.

In addition to the organic reactive compounds, other compounds have also shown efficacy against HD (inorganic compounds, polysilsesquioxanes, XE-555 resin), GD (OPAA enzymes, CLEC's) or both (dendrimers).

Both the reactive moieties described above as well as other compounds not listed were formulated into rTSP's at various loading percentages. The rTSP's are opaque white or off-white creams. As expected, FTIR analysis shows peaks in the region of C-O-C (1116 cm^{-1}), CF_2 (1198 cm^{-1}), and CF_3 (1259, 978 cm^{-1}) bands [10]. To evaluate the rTSP's we developed a Decision Tree Network that contains various *in vitro* and *in vivo* models [8]. We used a penetration cell test to measure the increase in protection of the rTSP versus the Topical Skin Protectant (Figure 2).

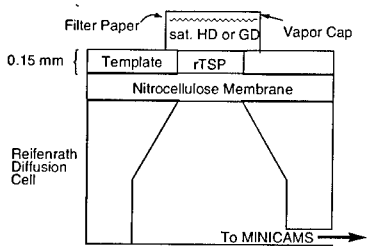


Figure 2. Schematic of penetration cell with saturated vapor setup.

The quantity of either GD or HD is periodically monitored using a miniature continuous air monitoring system (MINICAMS®) for 20 hours [11]. From these data, we obtain two values: the cumulative amount of CWA that penetrates through the rTSP; and the time at which a "break-through" occurs. We defined "break-through" values at the minimum amount of HD [12] and GD [13] (1000 ng) that results in a physiological response. These two values allow us to rank the rTSP formulations and to select the appropriate component for advanced development (Figure 3).

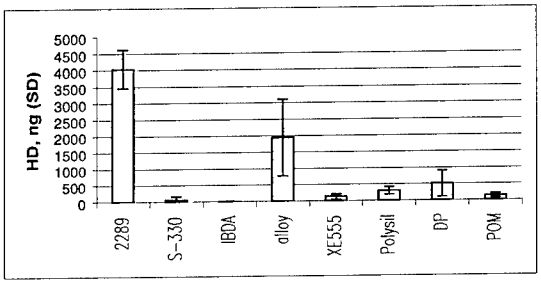
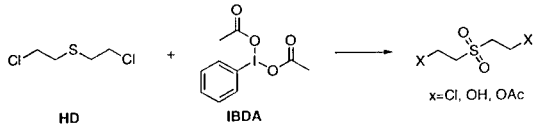


Figure 3. Cumulative amount of HD vapor through rTSP after 20 hours.

Small organic molecules S-330 and IBDA (see Figure 1) are among the most effective reactive components, reducing the amount of HD vapor by 98.5% and 99.7% relative to the TSP alone. S-330 reacts with HD to produce a variety of reaction products. [8, 14, 15] IBDA presumably oxidizes HD to give the non-toxic sulfoxide (Scheme 1).



Scheme 1. Oxidation neutralization of sulfur mustard by IBDA.

We also used the penetration cell to evaluate the increased protection offered by rTSP against GD vapor (Figure 4).

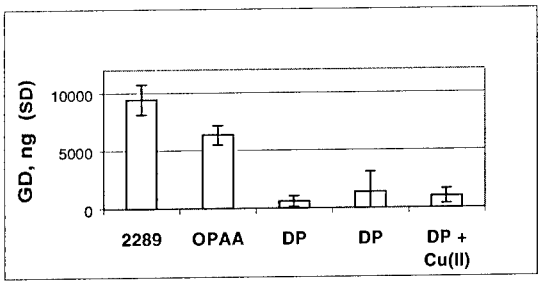
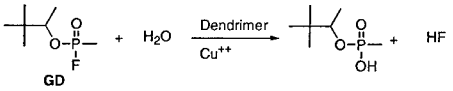


Figure 4. Cumulative amount of GD vapor through rTSP after 20 hours.

Against GD vapor, the most effective reactive components were OPAA enzymes (32% reduction), dendrimers (up to 94% reduction) and dendrimers with added Cu^{2+} (89% reduction).

All rTSP's that have shown efficacy against GD contain water, and thus we conclude that the reactive component acts as a catalyst for the hydrolysis of soman (Scheme 2).



Scheme 2. Hydrolyses of soman (GD) with dendrimer catalyst.

In preliminary studies of the hydrolysis of a GD simulant (diisopropylfluorophosphate, DFP), we have demonstrated that the hydrolysis of nerve agents is easily monitored by ^{31}P NMR (Figure 5).

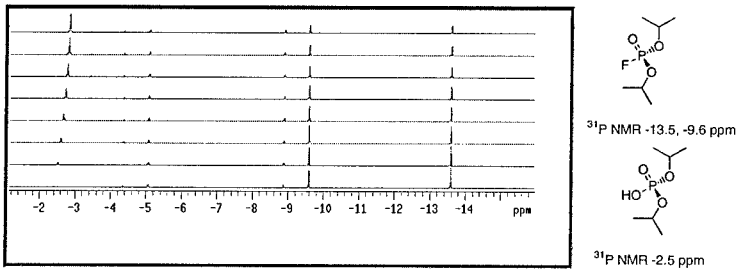


Figure 5. Hydrolysis of DPF with dendrimer monitored by ^{31}P NMR (starting at bottom of spectra, time = 0, 2, 4, 6, 8, 10, 14 hr).

In addition to the tests described above, we have also conducted extensive *in vivo* experiments. For example, we assessed the protection of the rTSP against HD vapor using a weanling pig model [8]. In this model, the protection afforded by the rTSP is correlated to the degree of erythema (Figure 6).

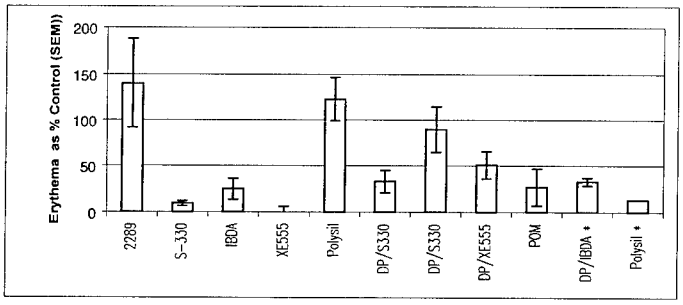


Figure 6. Protection of rTSP vs. HD vapor in weanling pig model (Control = no TSP).

A comparison of the animal data presented above and the penetration data presented in Figure 4 shows inconsistent results (Table II).

Table II. Contrasting efficacy against HD vapor penetration from *in vitro* and *in vivo* rTSP evaluation.

Reactive Component	Penetration Cell (ng at 20 hrs, % reduction.)	Weanling Pig (erythema, % of control)	Agreement
TSP	4037 ng, 0%	122%	Y
S330	60 ng, 98%	2.6%	Y
IBDA	9 ng, 99%	11%	Y
Dendrimer	507 ng, 88%	318%	N
Polysilsesquioxane	307 ng, 93%	123%	N
Polyoxometalate	130 ng, 96%	71%	N

Whereas reactive moieties such as small organic molecules (S-330 and IBDA) show protection in the penetration cell test and the weanling pig test, other classes of reactive moieties display seemingly contradictory results. As seen above, the rTSP's containing bridged polysilsequioxanes, dendrimers, and polyoxometalates reduced the cumulative amount of HD vapor in the penetration cell by 88-96%. However, the recorded erythema from HD vapor in these rTSP's is only slightly decreased or actually increased above control in the *in vivo* test. We have seen similar trends with other compounds and have four possible explanations. First, the skin is occluded by the rTSP, increasing agent penetration and thus the observed erythema. Second, the skin may be sensitized by the rTSP, and thus the small amount of HD vapor that penetrates the skin results in greater erythema. Third, the skin may be irritated by the reaction products. And fourth, agent may penetrate the rTSP during exposure and not be completely removed by the cleaning procedure.

CONCLUSION

We have reported the preparation and evaluation of Reactive Topical Skin Protectants. We developed these composite materials with optimum reactive compounds from the classes of small organic molecules, organic polymers, inorganic materials, and enzymes. Thus far, the optimum formulations display excellent resistance against GD (94% reduction of break-through after 20 hr) and HD (99% reduction in vapor break-through after 20 hours). These materials continue to move towards advanced development with the ultimate goal of complete protection for U.S. soldiers and civilians against CWA's.

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+ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council.

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